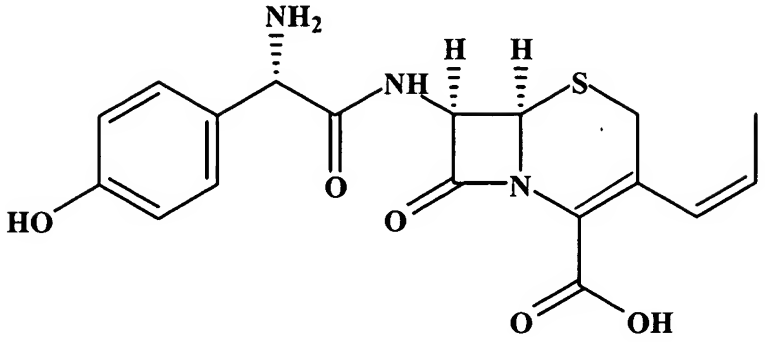
WE CLAIM

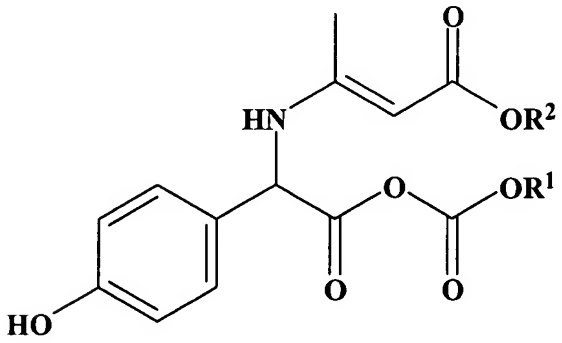
1. A process for preparation of Cefprozil of formula (I)



(I)

in the form of a monohydrate comprising of

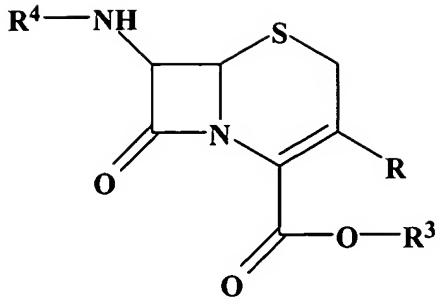
reacting a mixed acid anhydride of α-amino-p-hydroxy phenylacetic acid of formula (III)



(III)

wherein R^1 is an alkyl or an aryl group and R^2 is methyl or ethyl,

with a protected 7-amino-3-(propen-1-yl)-3-cephem-4-carboxylic acid of formula (VII)



(VII)

wherein R^3 and R^4 are protective groups,

followed by hydrolysis, isolation and purification to give Cefprozil of formula (I) in the form of a monohydrate in high yield and purity, substantially free of impurities.

2. A process as in claim 1 wherein

the mixed acid anhydride of α-amino-p-hydroxy phenylacetic acid of formula (III) is prepared by a process comprising the steps of

(a) adding an acylating agent and a base to a mixture of an inert organic solvent and a polar aprotic solvent at a temperature in the range of 0° to 40°C, preferably 20° to 25°C;
(b) cooling the solution to a temperature in the range of –70° to –30°C, preferably –35°C to –50°C;
(c) addition of Dane salt of an α-amino-p-hydroxy phenylacetic acid to the cooled solution and agitation at a temperature in the range of –70° to –30°C, preferably –35°C to –50°C.

3. A process as in claim 1 wherein

the mixed acid anhydride of α-amino-p-hydroxy phenylacetic acid of formula (III) is prepared by a process comprising the steps of

(a) adding an acylating agent and a base to an inert organic solvent at a temperature in the range of 0° to 40°C, preferably 20° to 25°C;

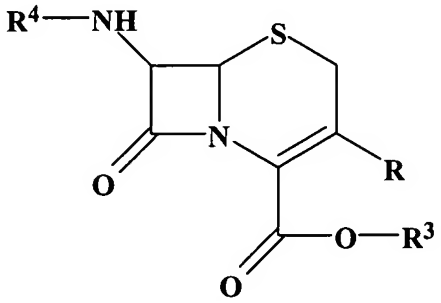
(b) cooling the solution to a temperature in the range of –70° to –30°C, preferably –35°C to –50°C;

(c) addition of Dane salt of an α-amino-p-hydroxy phenylacetic acid to the cooled solution and agitation at a temperature in the range of –70° to –30°C, preferably –35°C to –50°C.

(d) addition of a polar aprotic solvent to the above solution and agitation at a temperature in the range of –70° to –30°C, preferably –35°C to –50°C.

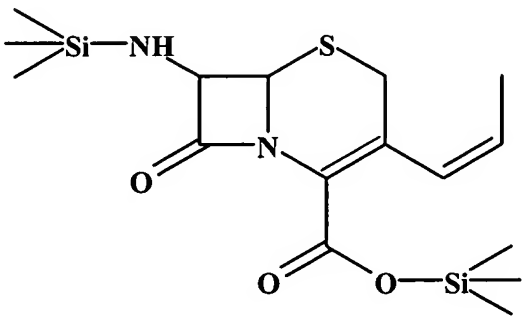
4. A process as in claim 1 wherein

the protected 7-APCA of formula (VII) used



(VII)

is such that R^3 and R^4 are each tri alkylsilyl group, and represented by formula (VI).



(VI)

5. A process according to claim 2, wherein the inert organic solvent employed in step i)(a) is selected from methylene chloride, tetrahydrofuran,

chloroform, diethyl ether, chlorotethane, acetonitrile, trichloroethylene, and ethyl acetate.

6. A process according to claim 3 , wherein the inert organic solvent employed in step i)(a) is selected from methylene chloride, tetrahydrofuran, chloroform, diethyl ether, chlorotethane, acetonitrile, trichloroethylene, and ethyl acetate

7. A process according to claim 2 , wherein the polar aprotic solvent employed in step i)(a) is selected from N,N-dimethyl formamide, acetone, acetonitrile, dimethyl sulphoxide and dimethyl acetamide. N,N-dimethyl formamide is the preferred polar aprotic solvent.

8. A process according to claim 3 , wherein the polar aprotic solvent employed in step i)(a) is selected from N,N-dimethyl formamide, acetone, acetonitrile, dimethyl sulphoxide and dimethyl acetamide. N,N-dimethyl formamide is the preferred polar aprotic solvent

9. A process according to claim 2 , wherein suitable acylating agents employed in step i)(a) is chosen from reactive forms of aliphatic, alicyclic, or aromatic acids such as chloroformic acid, benzoic acid, pivalic acid and 2-ethylhexanoic acid. The reactive forms of these acids include their esters such as ethyl chloroformate, isobutyl chloroformate and their halogenides like pivaloyl chloride, 2-ethyl-hexanoyl chloride and benzoyl chloride, the preferred acylating agent being ethyl chloroformate.

10. A process according to claim 3, wherein suitable acylating agents employed in step i)(a) is chosen from reactive forms of aliphatic, alicyclic, or aromatic acids such as chloroformic acid, benzoic acid, pivalic acid and 2-ethylhexanoic acid. The reactive forms of these acids include their esters such as ethyl chloroformate, isobutyl chloroformate and their halogenides like pivaloyl chloride, 2-ethyl-hexanoyl chloride and benzoyl chloride, the preferred acylating agent being ethyl chloroformate.

11. A process according to claim 2, wherein the base employed in step i)(a) is selected from triethylamine, picoline, N-methylmorpholine, N,N-dimethylbenzylamine, lutidine, N,N-dimethyl-4-aminopyridine, N,N-dicyclohexylamine, the preferred base being N-methylmorpholine.

12. A process according to claim 3, wherein the base employed in step i)(a) is selected from triethylamine, picoline, N-methylmorpholine, N,N-dimethylbenzylamine, lutidine, N,N-dimethyl-4-aminopyridine, N,N-dicyclohexylamine, the preferred base being N-methylmorpholine.

13. A process according to claim 2, wherein the acylating agent employed in step i)(a) is employed preferably in the range of 1to1.5 moles per mole of Dane salt.

14. A process according to claim 3, wherein the acylating agent employed in step i)(a) is employed preferably in the range of 1to1.5 moles per mole of Dane salt.

15. A process according to claim 2 , wherein the base employed in step i)(a) is employed preferably in the range of 0.02 to 0.04 moles per mole of Dane salt.

16. A process according to claim 3, wherein the base employed in step i)(a) is employed preferably in the range of 0.02 to 0.04 moles per mole of Dane salt..

17. A process according to claim 2 wherein the temperature in step i)(a) is preferably 20° to 25°C.

18. A process according to claim 3 wherein the temperature in step i)(a) is preferably 20° to 25°C

19. A process according to claim 2 wherein the Dane salt is preferably sodium or potassium D-N- (1-methoxycarbonylpropene-2-yl)-α-amino-p-hydroxyphenyl

acetate or sodium or potassium D-N-(1-ethoxycarbonylpropene-2-yl)-α-amino-p-hydroxyphenyl acetate.

20. A process according to claim 3 wherein the Dane salt is preferably sodium or potassium D-N- (1-methoxycarbonylpropene-2-yl)-α-amino-p-hydroxyphenyl acetate or sodium or potassium D-N-(1-ethoxycarbonylpropene-2-yl)-α-amino-p-hydroxyphenyl acetate

21. A process according to claim 2 wherein the temperature in step i)(c) is preferably –35°C to –50°C.

22. A process according to claim 3 wherein the temperature in step i)(c) is preferably –35°C to –50°C

23. A process according to claim 2 wherein the temperature in step i)(d) is preferably –35°C to –50°C.

24. A process according to claim 3 wherein the temperature in step i)(d) is preferably –35°C to –50°C

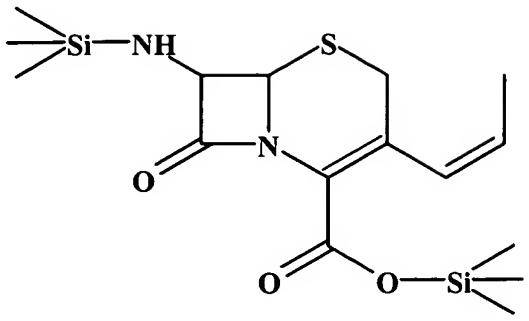
25. A process according to claim 1 wherein the mixed acid anhydride is condensed with protected 7-APCA at a temperature preferably in the range of –90° to –30°C.

26. A process according to claim 1 wherein the mixed acid anhydride is condensed with protected 7-APCA at a temperature most preferably in the range –50° to –40°C.

27. A process according to claim 25 wherein the mixed acid anhydride is condensed with protected 7-APCA at a temperature most preferably in the range –50° to –40°C.

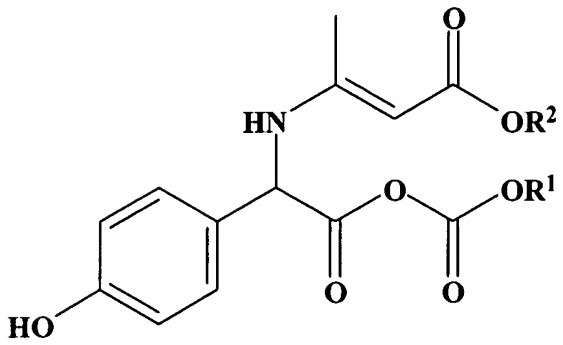
28. A silylated 7-amino-3-(propen-1-yl)-3-cephem-4-carboxylic acid compound of

formula (VI).



(VI)

29. A mixed acid anhydride of formula (III)



(III)

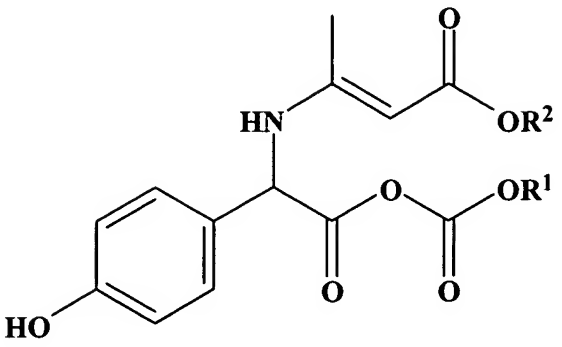
prepared by a process comprising the steps of

(a) adding an acylating agent and a base to a mixture of an inert organic solvent and a polar aprotic solvent at a temperature in the range of 0° to 40°C, preferably 20° to 25°C;

(b) cooling the solution to a temperature in the range of –70° to –30°C, preferably –35°C to –50°C;

(c) addition of Dane salt of an α-amino-p-hydroxy phenylacetic acid to the cooled solution and agitation at a temperature in the range of –70° to –30°C, preferably –35°C to –50°C.

30. A mixed acid anhydride of formula (III)



(III)

prepared by a process comprising the steps of

(a) adding an acylating agent and a base to an inert organic solvent at a temperature in the range of 0° to 40°C, preferably 20° to 25°C;

(b) cooling the solution to a temperature in the range of –70° to –30°C, preferably –35°C to –50°C;

(c) addition of Dane salt of an α-amino-p-hydroxy phenylacetic acid to the cooled solution and agitation at a temperature in the range of –70° to –30°C, preferably –35°C to –50°C.

(d) addition of a polar aprotic solvent to the above solution and agitation at a temperature in the range of –70° to –30°C, preferably –35°C to –50°C.